KaSim reference manual v1.05

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This document is work in progress...

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Chapter 1

Introduction

1.1 Preamble

This manual contains a description of the usage of KaSim. Although it contains a brief description of Kappa, it is *not* intended as a Kappa tutorial. Therefore, in the following of this manual some familiarity with Kappa is assumed and we let the reader refer to `http://KappaLanguage.org` for further explanations.

1.2 The KaSim engine

KaSim is an open source stochastic simulator of rule-based models [3, 2, 4] written in the κ-calculus. Basically KaSim takes one or several kappa files as inputs and generates stochastic trajectories of various observable. KaSim implements the network free simulation algorithm for rule-based models [1] that extends Gillespie's algorithm [5, 6].

A *simulation event* corresponds to the application of a rewriting rule, contained in the kappa file, to the current graph (also called a *mixture*). The rule is selected according to its *activity*, *i.e* the number of instances it has in the current mixture, multiplied by its kinetic rate, and applied one of its possible instance in the graph. It results in a new graph together with an updated activity for all rules (see Fig. 1.1).

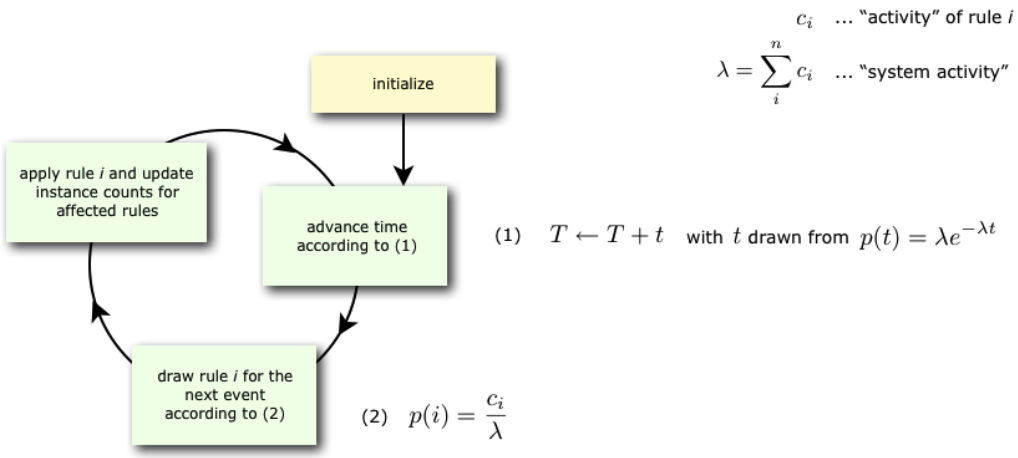

Figure 1.1: The event loop

Importantly, the cost of such an event is independent of the size of the graph it is applied to [1]. Note that KaSim is not equipped with a curve visualization tool. However, the outputted data are in text format and usable with any standard plotting software such as GnuPlot.

1.3 Support

- Kappa language tutorials and downloads: `http://kappalanguage.org`
- Bug reports should be posted on github: `https://github.com/jkrivine/KaSim/issues`
- Questions and answers on the kappa-user mailing list: `http://groups.google.com/group/kappa-users`
- Want to contribute to the project? `jkrivine` at `pps` dot `jussieu` dot `fr`

Chapter 2

Installation

2.1 Obtaining the sources

To obtain KaSim you can either use pre-compiled binaries available on KappaLanguage.org or compile the sources for your architecture. To do so, download the source code from `https://github.com/jkrivine/KaSim` and make sure you have a recent ocaml compiler installed. From a terminal window type `ocamlopt.opt -v`. If nothing appears then you need to install Ocaml Native compiler that can be downloaded from `http://caml.inria.fr/download.en.html`.

2.2 Compilation

Once Ocaml is safely installed, untar KaSim archive and compile following these few steps:

```
$ tar xzvf kasim.tar.gz -d Kappa
$ cd Kappa
$ make
```

At the end of these steps you should see, in the `Kappa` directory, an executable file name KaSim. In order to check the compilation went fine, simply type `.\KaSim -version`. If the ocaml native compiler `ocamlopt.opt` is not in the path of your system, you may set the variable `OCAMLBINPATH` to point to the location of the compiler by editing the corresponding line in the Makefile.

Chapter 3

The command line

3.1 General usage

From a terminal window, KaSim can be invoked by typing

```
$ KaSim -i file_1 ...  -i file_n [option]
```

where `file_i` are the input kappa files containing the rules, initial conditions and observable see Chapter 4 below. Tables 3.1 and 3.2 summarize all the options that can be given to the simulator. Basically one should specify an upper bound either in bio time (arbitrary time unit), or number of events. Note that bio-time is computed using Gillespie's formula for time advance (see Fig. 1.1) and should not be confused with CPU-time (it's not even proportional). In doubt we recommend using a bound in number of events since the cost of one event application is bounded (in CPU time) by a constant, so the simulation time of n events is roughly k times the simulation time of $k * n$ events.

3.2 Main options

Table 3.1: Command line: main options

Argument	Description
`-e` e_{max}	Terminates simulation after $e_{max} \geq 0$ events
`-t` t_{max}	Terminates simulation after $t_{max} \geq 0.0$ time units
`-p` n	Produces a data file (default: `data.out`) with $n \geq 0$ data points
`-o` *file*	Set the name of data file to *file*
`-d` *dir*	Redirects all output files to the directory *dir*

3.3 Advanced options

Table 3.2: Command line: advanced options

Argument	Description
`-seed` n	Seeds the pseudo-random number generator $n > 0$
`-implicit-signature`	Automatically deduce agent signatures

Example

The command

```
$ KaSim -i model.ka -e 1000000 -p 1000 -o model.out
```

will generate a file `model.out` containing the trajectories of the observables defined in the kappa file `model.ka`. The file `model.out` will contain a 1000 data point (*i.e* in this case, a measure will be taken every 1000 events). The command

```
$ KaSim -i init.ka -i rules.ka -i obs.ka -i mod.ka -t 1.5 -p 1000
```

will generate a file `data.out` (default name) containing 1000 data points of a simulation of 1.5 seconds (arbitrary time units) of the model. Note that the input kappa file is splited in 4 files containing, for instance, the initial conditions, `init.ka`, the rule set, `rules.ka`, the observables, `obs.ka`, and the perturbations, `pert.ka` (refer to Chapter 4 for details). Note that the order in which the files are given does not matter.

Chapter 4

The kappa file

4.1 General remarks

The *Kappa File* (KF) is the formal representation of your model. We use KF to denote the union of the files that are given as input to KaSim (argument `-i`). Each line of the KF is interpreted by KaSim as a *declaration*. If the line is ended by the escape character '\' the continuation of the declaration is parsed onto the next line. Declarations can be of 4 types: *signatures* (Sec. 4.2), *rules* (Sec. 4.3), *variables* (Sec. 4.4), *initial conditions* (Sec. 4.5) and *perturbations* (Sec. 4.6). The KF's structure is quite flexible since it can be divided in any sub-files and the order in which declarations are entered does not matter.

4.2 Agent signature

Agent signatures constitute a form of typing information about the agents that are used in the model. It contains information about the name and number of interaction sites the agent has, and about their possible internal states. A signature is declared in the KF by the following line:

`%agent:` *signature_expression*

according to the grammar given Table 4.1. For instance the line:

signature_expression	::=	*Id* (*sig*)
sig	::=	*Id* *internal_state_list*, *sig* | ε
internal_state_list	::=	~*Id* *internal_state_list* | ε

Table 4.1: Agent signature expression: terminal symbol are denoted in blue. Symbol *Id* can be any string generated by regular expression [*a*-*z* *A*-*Z* 0-9][*a*-*z* *A*-*Z* 0-9 _ −]*. Terminal symbol ε stands for the empty symbol.

```
%agent:  A(x,y~u~p,z~0~1~2)
```

will declare an agent `A` with 3 *(interaction) sites* `x,y` and `z` with the site `y` possessing two *internal states* `u` and `p` (for instance for the unphosphorylated and phosphorylated forms of `y`) and the site `z` having possibly 3 states respectively 0, 1 and 2. Note that internal states values are treated as untyped symbols by KaSim, so choosing a character or an integer as internal state is purely matter of convention.

4.3 Rules

Once agents are declared, one may add to the KF the rules that describe their dynamics through time. Roughly a Kappa rule looks like

`'my rule'` *kappa_expression* $\rightarrow$ *kappa_expression* `@` k

where `'my rule'` can be any name that will refer to the subsequent rule that can be decomposed into a *left hand side* (LHS) and a *right hand side* (RHS) kappa expressions together with a *kinetic rate* k. Kappa expressions are generated by the grammar given Table 4.2.

kappa_expression	::=	*agent_expression* , *kappa_expression* $\mid \varepsilon$
agent_expression	::=	*Id* (*interface*)
radius	::=	$\varepsilon \mid \{n\}$
interface	::=	$\varepsilon \mid$ *site internal_state link_state*
internal_state	::=	$\varepsilon \mid \sim$ *Id*
link_state	::=	$\varepsilon \mid$!n | !_ | ?

Table 4.2: Kappa expressions: In addition to the conventions of Table 4.1, symbol n denotes any positive integer.

4.3.1 A simple rule

With the signature of `A` defined in the previous section, the line

```
'A dimerization' A(x),A(y~p) → A(x!1),A(y~p!1) @ k
```

denotes a dimerization rule between two instances of agent `A` provided the second is phosphorylated (say that is here the meaning of `p`) on site `y`. Note that the bond between both `A`s is denoted by the identifier `!1` which uses an arbitrary integer (`!0` would denote the same bond. In Kappa, a bond may connect exactly 2 sites so any occurrence of a bond identifier `!`n has to be paired with exactly one other sibling in the expression. Note also the fact that site `z` of `A` is not mentioned in the expression which means that it has no influence on the triggering of this rule. This is the *don't care don't write convention* (DCDW) that plays a key role in resisting combinatorial explosion when writing models.

4.3.2 Adding and deleting agents

Sticking with A's signature, the rule

'budding A' A(z) → A(z!1),A(x!1) @ k

indicates that an agent A free on site z, no matter what its internal state is, may beget a new copy of A bound to it *via* sites x. Note that in the RHS, agent A's interface is not completely described. Following the DCDW convention, KaSim will then assume that the sites that are not mentioned are created in the *default state*, *i.e* the appear free of any bond and their internal state (if any) is the first of the list shown in the signature (here state u for y and 0 for z).

Importantly, KaSim respects the *longest prefix convention* to determine which agent in the RHS stems from an agent in the LHS. In a word, from a rule of the form $a_1, \ldots, a_n \to b_1, \ldots, b_k$, with a_is and b_js being agents, one computes the biggest indices $i \leq n$ such that the agents $a_1, \ldots, a_i$ are pairwise consistent with $b_1, \ldots, b_i$, *i.e* the a_js and b_js have the same name and the same number of sites. In which case we say that the for all $j \leq i$, a_j is *preserved* by the transition and for all $j > i$, a_j is *deleted* by the transition and b_j is *created* by the transition. This convention allows us to write a deletion rule as:

'deleting A' A(x!1),A(z!1) → A(x) @ k

4.3.3 Side effects

It may happen that the application of a rule has some *side effects* on agents that are not mentioned explicitly in the rule. Consider for instance the previous rule

'deleting A' A(x!1),A(z!1) → A(x) @ k

Since the A in the graph that is matched to the second occurrence of A in the rule will be deleted, as a consequence all its sites will be deleted accordingly. In entails that when applied to the graph G =A(x!1,y~p,z~2),A(x!2,y~u,z~0!1),C(t!2) it results in a new graph G' = A(x!1,y~p,z~2),C(t) where the site t of C is freed as side effect.

Wildcard symbols for link state ? (for bound or not), !_ (for bound to someone), may also induce side effects when they are not preserved in the RHS of a rule, as in

'Disconnect A' A(x!_) → A(x) @ k

or

'Force bind A' A(x?) → A(x!1),C(t!1) @ k

Both these rule will cause KaSim to raise a warning at rule compile time.

4.3.4 Kinetic rates

4.4 Variables

4.5 Initial conditions

4.6 Perturbation language

Bibliography

[1] Vincent Danos, Jérome Féret, Walter Fontana, and Jean Krivine. Scalable simulation of cellular signaling networks. In *Proceedings of APLAS'07: 5^th ASIAN symposium on programming languages and systems*, volume 4807 of *LNCS*, pages 139–157, 2007. Invited paper.

[2] Vincent Danos, Jérôme Feret, Walter Fontanta, Russ Harmer, and Jean Krivine. Rule based modeling of biological signaling. In Luís Caires and Vasco Thudichum Vasconcelos, editors, *Proceedings of CONCUR 2007*, volume 4703 of *LNCS*, pages 17–41. Springer, 2007.

[3] Vincent Danos and Cosimo Laneve. Formal molecular biology. *Theoretical Computer Science*, 325, 2004.

[4] James R. Faeder, Mickael L. Blinov, and William S. Hlavacek. Rule based modeling of biochemical networks. *Complexity*, pages 22–41, 2005.

[5] Daniel T. Gillespie. A general method for numerically simulating the stochastic time evolution of coupled chemical reactions. *Journal of Computational Physics*, 22(4):403–434, 1976.

[6] Daniel T. Gillespie. Exact stochastic simulation of coupled chemical reactions. *Journal of Physical Chemistry*, 81(25):2340–2361, 1977.